Heparin-Induced Thrombocytopenia

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Heparin-Induced Thrombocytopenia

Objectives

I. Review the mechanisms of action of heparin and its reversal
II. Understand the physiologic/pathologic alterations seen with Heparin-Induced Thrombocytopenia (HIT)
III. Management strategies for patients with HIT requiring anticoagulation for cardiac surgery

Heparin

The anticoagulant of choice when a rapid anticoagulant effect is required

- Onset of action is immediate when administered by IV injection
- Inexpensive
- Reversible
- Great amount of familiarity with its use
- Generally well tolerated

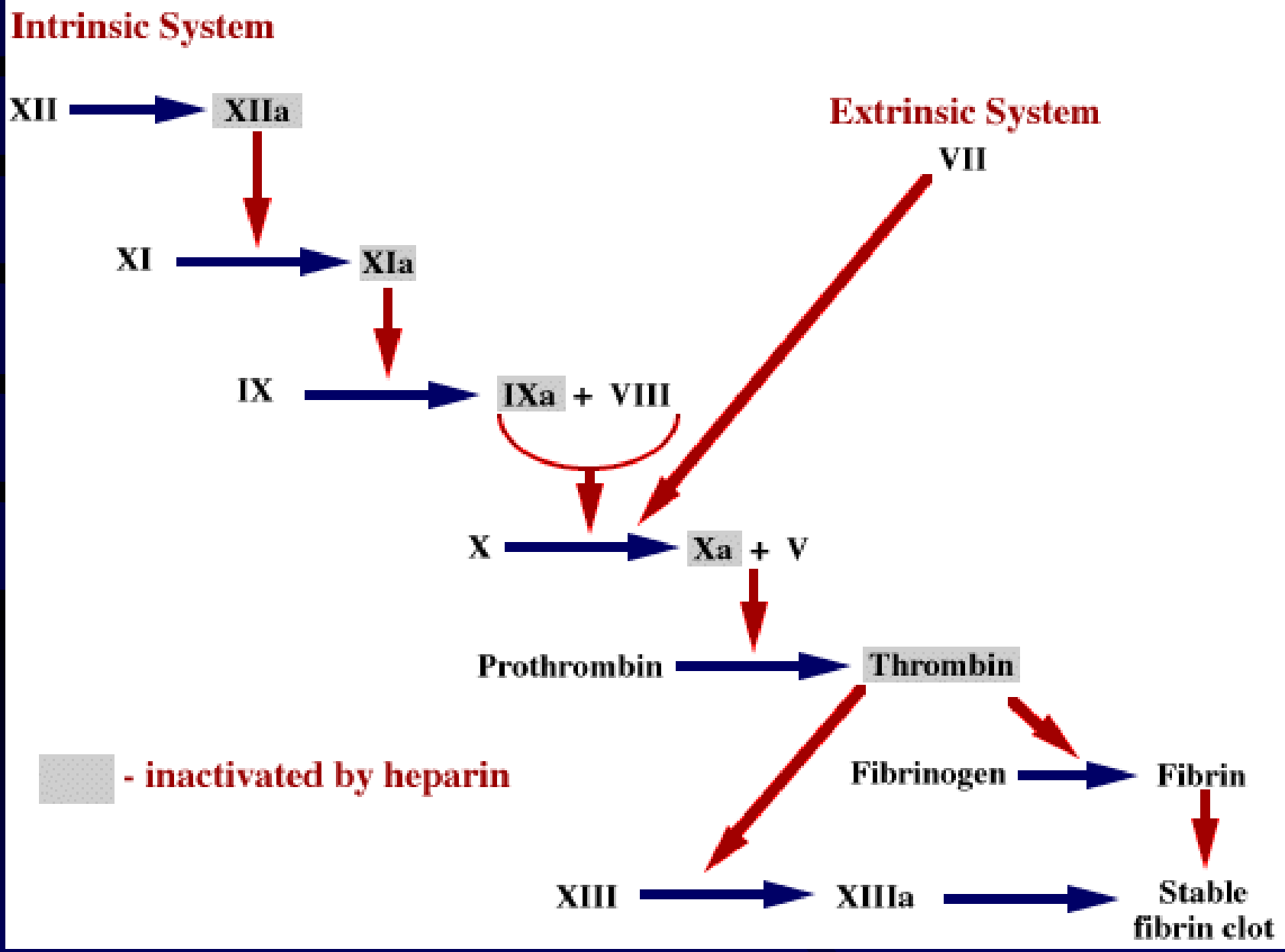
Heparin

- A heterogeneous group of polyanionic sulfated glycosaminoglycans with a unique pentasaccharide sequence that interacts with the anticoagulant antithrombin III (AT)
- Mean molecular weight 15,000 d (range 3000-30,000 d)
- Only 1/3 of heparin molecules contain the high-affinity pentasaccharide sequence required for anticoagulant activity

Coagulation Cascade

- Most clotting factors circulate in an inactive form (procoagulant)
- A portion of protein is cleaved off to form an active enzyme (a serine protease)
- AT covalently binds to and inactivates serine proteases on coagulation factors IIa, IXa, Xa, XIa, and XIIa to regulate coagulation

Coagulation Cascade and the use of Heparin

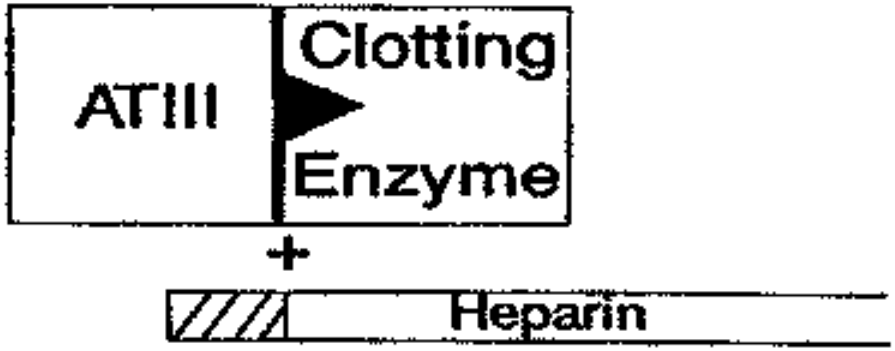


Heparin/AT Interaction

- Heparin binds to a lysine site on AT, inducing a conformational change at the clotting factor binding site
- This converts AT from a slow, progressive clotting factor inhibitor to a very rapid inhibitor of thrombin and factor Xa
- Heparin then dissociates from the complex and can be reutilized

Without Heparin

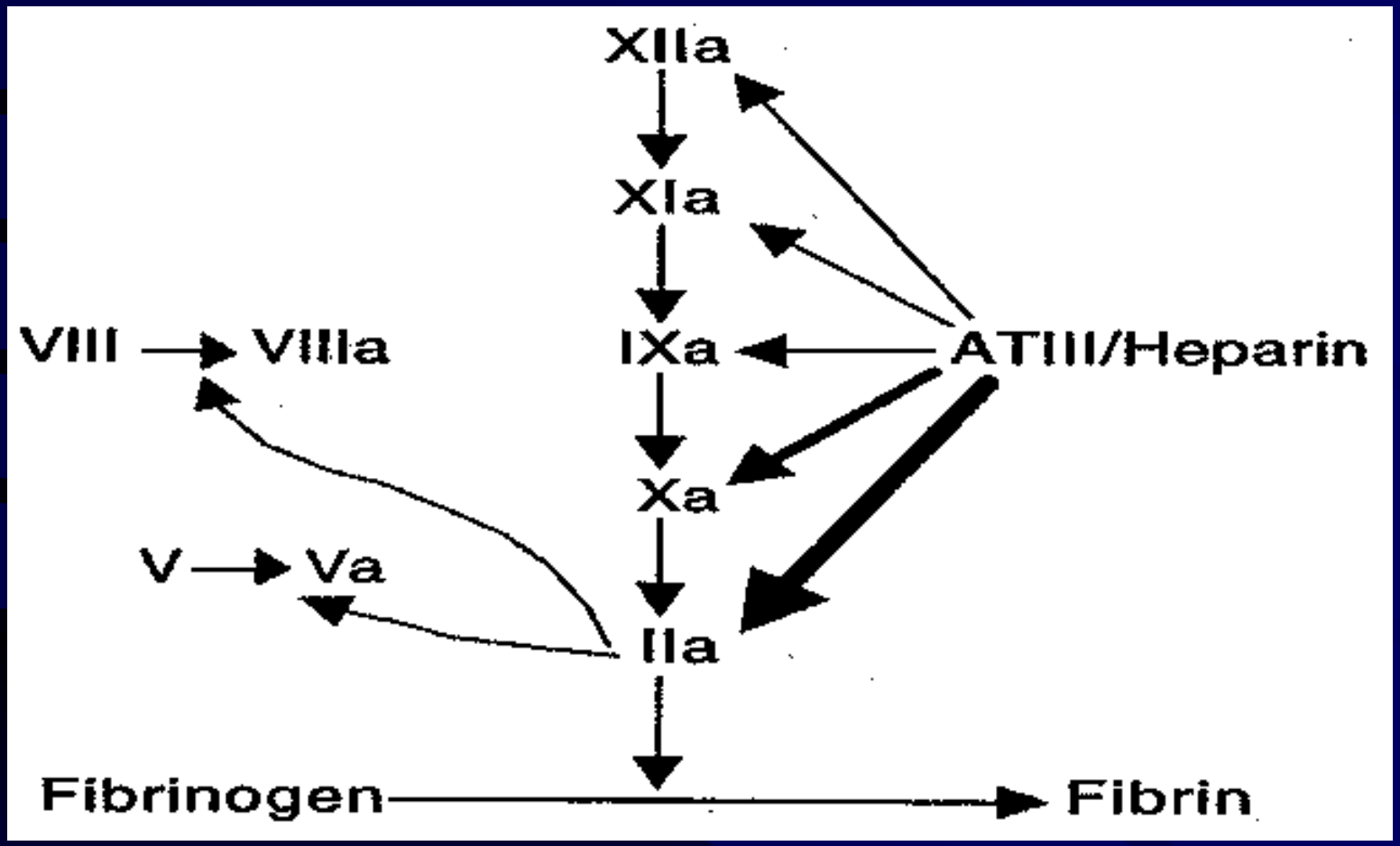
Ternary Complex Formation



Dissociation of Heparin

Heparin/AT Interaction

- Thrombin and factor Xa are most responsive to inhibition, thrombin being ~10-fold more sensitive to inhibition than Xa
- Other heparin mechanisms of action include binding directly to platelets and binding cofactor II


XIIa
XIa
VIII
VIIIa
IXa
ATIII/Heparin
Xa
V
Va
IIa
Fibrinogen
Fibrin

Heparin Pharmacokinetics

- Large molecular size and polarity limits distribution to intravascular space and endothelial cells
- Anticoagulant response is variable due to binding to a number of plasma proteins, endothelial cells, and macrophages

Heparin Resistance

- Higher than average doses of heparin required to achieve the expected anticoagulation effect
- Multiple causes, including: AT deficiency, increased heparin clearance, elevations in heparin binding proteins, factor VIII, fibrinogen, and platelet factor 4 (PF4)
- Reports of heparin resistance induced by aprotinin and nitroglycerin

Heparin Pharmacokinetics

- Clearance involves a combination of:

1. Rapid, saturable phase through binding to receptors on endothelial cells and macrophages →metabolism in the reticuloendothelial system

   - (main mechanism of clearance of therapeutic doses→half-life increases with increasing dose)

2. Slower first-order renal elimination

Heparin Dose vs. Plasma $t_{1/2}$

Heparin Dose	Half-Life
25 U/kg	30 min
100 U/kg	60 min
400 U/kg	150 min

Heparin Reversal

- Protamine - A cationic protein derived from fish sperm that binds to and inactivates heparin (approx 100 U UFH/mg protamine)
- Protamine-heparin complexes are cleared from circulation

Protamine – Adverse Reactions

1. Hypotension due to systemic vasodilation (non-histamine-mediated)
2. Anaphylactic
3. Anaphylactoid
4. Pulmonary vasoconstriction – can lead to Rt ventricular failure, decreased CO, systemic hypotension

Protamine – Adverse Reactions

Patients at potential risk for true allergy to protamine	
Condition	Risk increase
Prior reaction to protamine	189-fold
Exposure to NPH insulin	8.2-fold
Allergy to any drug	3.0-fold
Prior exposure to protamine	No increase!

Heparin – Adverse Reactions

- Hemorrhage
- Hypotension due to decreased SVR with bolus dosing
- Anaphylaxis (rare)
- Altered concentrations of lipid-soluble drugs due to activation of lipoprotein lipase
- Osteoporosis (with long-term use)

Heparin-Induced Thrombocytopenia (HIT)

- A decrease in platelet count induced by the administration of heparin for therapeutic purposes
- 2 Types
  1. Type I, non-immune, Heparin-Associated Thrombocytopenia (HAT)
  2. Type II, immune, Heparin-Induced Thrombocytopenia (HIT), Heparin-Induced Thrombocytopenia and Thrombotic Syndrome (HITTS)

HIT Type I

- Mild thrombocytopenia, rapid onset (within 2-5 days of starting heparin)
- The result of a direct agglutination effect of heparin on platelets
- Not immune-mediated, does not cause thrombosis
- Self-resolving, even if heparin is continued

HIT Type II

- Generally presents as an unexpected platelet count fall beginning 5-10 days after heparin exposure
- May be seen within hours in patients exposed to heparin within the past 100 days (usually within past 3 weeks)

Heparin-Induced Thrombocytopenia (HIT)

- Thrombocytopenia is usually moderate severity
- 80% of patients have platelet count nadirs between 20K-150K (median 60K)
- 10% have platelet counts below 20K
- 10% never fall below 150K

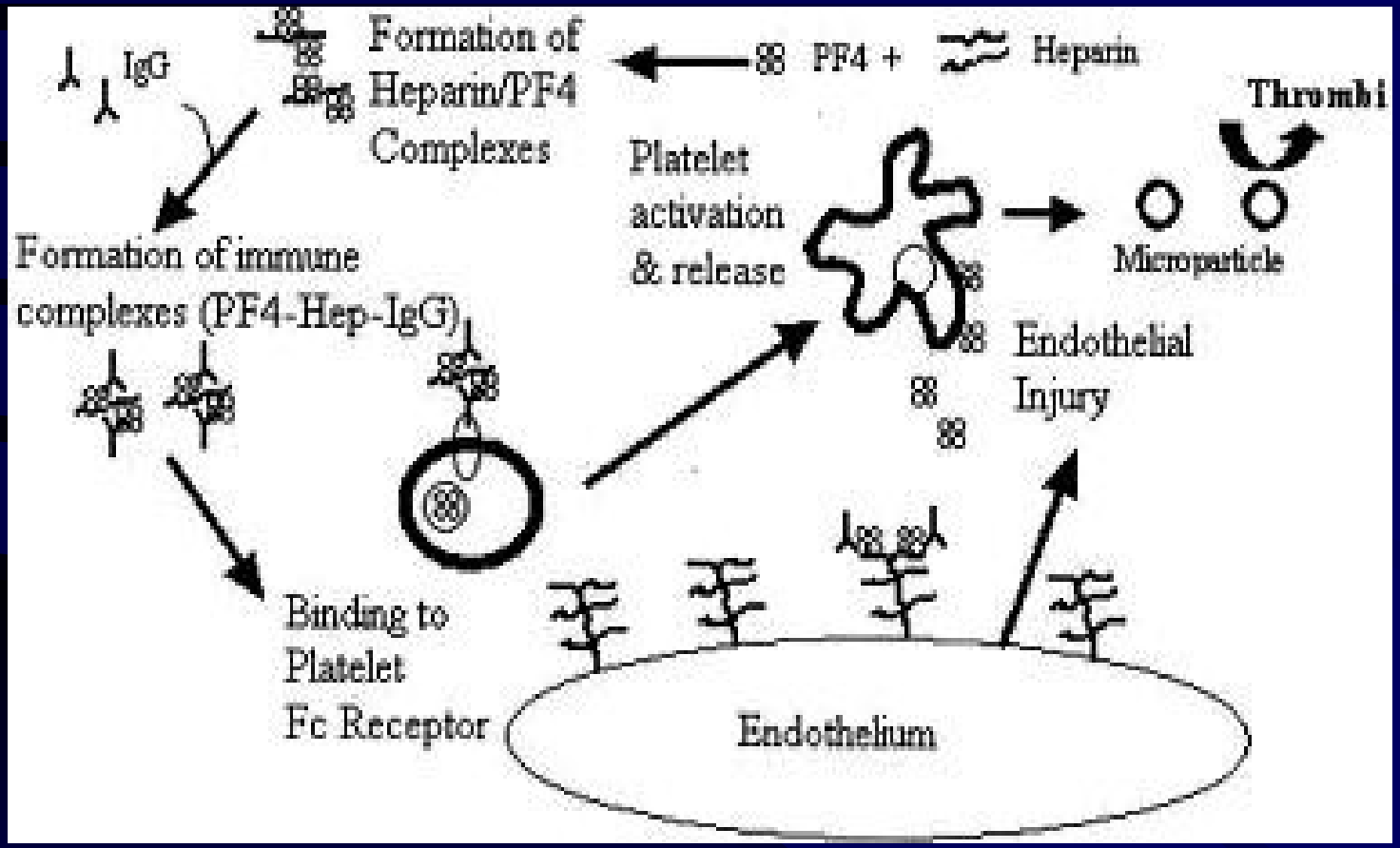
HIT - Epidemiology

- 25-50% of post-cardiac surgery patients exposed to heparin develop detectable antibodies by ELISA, <10% of these develop clinical HIT
- Overall incidence 1-3%
- Beef lung heparin more likely than porcine gut to cause HIT

HIT - Pathophysiology

- Immune mediated
- IgG antibodies form against heparin-platelet factor 4 complexes
- Binding of IgG to Fc receptor of circulating platelets → signal transduction and cell activation → platelet agglutination and lysis
- PF4 can also bind to endothelial cells, providing targets for antibody binding and local injury

HIT - Pathophysiology



HIT - Pathophysiology

- Ag/Ab complexes interact with platelets and endothelial cells, resulting in release of platelet microparticles, thromboxane, and **massive thrombin generation**
- Patients with HIT are at risk of developing venous & arterial thromboses, localized skin lesions, end-organ failure
- Thrombosis typically characterized by presence of white clots rich in platelets (white clot syndrome)

HIT - Pathophysiology

- Overt DIC occurs in 5-10% of HIT patients
- Rapid-onset HIT after bolus heparin can manifest an acute systemic reaction; Sx:
  - Inflammatory (fever, chills, flushing)
  - Cardiorespiratory (dyspnea, hypertension, cardiorespiratory arrest)
  - Gastrointestinal (vomiting, diarrhea)
  - Neurologic (transient global amnesia)

HIT - Thrombosis

- 40-75% of patients with HIT develop thrombosis
- Predominance of venous over arterial thrombosis (2:1 to 4:1)
  - DVT (UE & LE), PE; intra-atrial, intra-ventricular, mesenteric, brachial, renal, spinal, sinus vein, adrenal veins
- Arterial thrombi predominate in postcardiac surgery patients (atherosclerosis, A-lines, IABPs)
  - Large leg vessels, CVA, MI, saphenous vein graft occlusion

HIT – Morbidity/Mortality

- Early studies reported the mortality of HIT as 23-61%
- Early diagnosis and treatment have reduced mortality to 1.1-7.4%
- Amputations in HIT remain approximately 25%

HIT - Diagnosis

- A clinicopathologic diagnosis: requiring both a positive diagnostic test and the appropriate clinical setting
- HIT should be suspected in any patient who develops a 50% reduction of platelet count while on heparin treatment

HIT – Laboratory Diagnosis

- HIT assays are often sent to diagnostic labs
  - If a strong clinical suspicion of HIT, do not delay treatment while waiting for lab results

1. ELISA – detects binding of antibody to heparin/PF 4 complexes
   - High sensitivity, moderate predictive value
2. Functional Assays –
   - similar sensitivity to ELISA, improved specificity

HIT – Laboratory Diagnosis

- Functional assays
  1. Platelet aggregation test
     - platelet-poor plasma from the patient mixed with normal donor platelets and heparin
     - Plasma with HIT causes activation and aggregation of platelets
  2. ^{14}C-serotonin release test
     - Healthy donor platelets are incubated with ^{14}C-serotonin, which is taken up by the platelet membrane
     - After washing, the platelets are mixed with the serum to be tested and with heparin
     - Plasma with HIT increases the release of serotonin

HIT - Management

- If there is a strong suspicion of immune HIT, therapeutic management should be started immediately:
  1. Removal of the immune stimulus by eliminating all sources of heparin (line flushes, LMWH, heparin-coated catheters)
  2. Inhibition of thrombin generation with non-heparin anticoagulants

HIT - Management

3. Lower extremities (& upper if central venous catheters) should be screened for DVT
4. Consider adjunctive therapies (e.g., surgical thromboembolectomy for limb-threatening arterial thrombosis)
5. Platelet transfusions for bleeding prophylaxis are relatively contraindicated

HIT – Anticoagulation

- LMWH
  - Has been used in treatment of HIT in the past
  - High rate of cross-reactivity between LMWH & HIT Ab (34% with enoxaparin, 25.5% with dalteparin)
  - Should not be used unless antibody cross-reactivity is excluded

HIT - Anticoagulation

- Warfarin
  - Should be avoided during acute HIT
  - Depletion of protein C anticoagulant can lead to limb necrosis resulting from microvascular thrombosis – usually seen when INR rises above 3.5 (correlates with protein C depletion)
  - If long-term anticoagulation is needed, warfarin can be started after platelet count recovery and needs to overlap at least 5 days with the heparin alternative being used

HIT - Anticoagulation

- Danaparoid
  - Initial mainstay in HIT management, no longer available in US
  - Mixture of heparan sulfate, dermatin sulfate, and chondroitan sulfates
  - Cross-reactivity with heparin-dependent antibodies can occur, but is usually clinically insignificant
  - Treatment monitored by anti Xa activity
  - Long half life (24 hrs), renally cleared, use cautiously in renal failure

HIT - Anticoagulation

- Thrombin inhibitors
  - Chemically unrelated to heparin
  - No cross-reactivity with heparin-dependent antibodies

1. Argatroban
2. Lepirudin
3. Bivalirudin

Argatroban

- Synthetic L-arginine derivative
- Exerts its anticoagulant effects by competitively and reversibly inhibiting thrombin
- Binds directly to the catalytic site of thrombin, independently of AT III

Argatroban

- PTT is used for monitoring effect (PT is also prolonged – can complicate warfarin initiation)
- Hepatically metabolized, can be used in renal dysfunction
- With normal hepatic function, half-life ranges from 39-51 minutes

Lepirudin

- Recombinant hirudin – a 65-amino acid polypeptide secreted by the salivary glands of the medicinal leech
- Most potent natural thrombin inhibitor known
- A bivalent thrombin inhibitor – interacts with both the fibrinogen-binding and catalytic sites of thrombin→completely inhibits all of thrombin's procoagulant effects
- Binds to and inhibits both soluble and clot-bound thrombin

Lepirudin

- Renally cleared, dose adjustments needed for patients with renal insufficiency
- Half-life ranges from 80 minutes (normal renal function) to more than 200 hours (anephric patients)
- Therapy is monitored with PTT (goal 2.5x normal)
- 40% of patients develop antihirudin antibodies – can delay renal elimination and increase effect – ongoing monitoring is recommended

Lepirudin

- No antidote is available
- High risk of bleeding with supratherapeutic levels
- In cases of severe bleeding, modified ultrafiltration, hemofiltration, and hemodialysis have been used to reduce lepirudin concentrations
- Risk of anaphylaxis, especially on re-exposure

Bivalirudin

- A synthetic 20-amino acid peptide of two short hirudin peptide fragments connected by a tetraglycine spacer
- Neutralizes the fibrinogen binding site and catalytic site of thrombin
- Lower rate of hemorrhage than lepirudin

Bivalirudin

- Reversible thrombin inhibitor
- Half-life of 25 minutes (normal renal function)
- Clearance predominantly mediated by proteolytic cleavage by plasma enzymes (80%), remainder is renal (20%)

Anticoagulation for Cardiopulmonary Bypass (CPB)

- Mandates high-dose anticoagulation
  - Activation of coagulation by contact of blood with the artificial surfaces of the CPB apparatus
  - Reinfusion of tissue factor-enriched blood from the operative field

Anticoagulation for Cardiopulmonary Bypass (CPB)

- Advantages of heparin during CPB:
  1. High efficacy for preventing thrombosis of the CPB circuit
  2. Rapid and simple intraoperative monitoring by activated clotting time
  3. Neutralization by protamine

Management of patients with HIT requiring anticoagulation for CPB

- Situations in which heparin is truly contraindicated must be well defined
- HIT antibodies are transient – usually decline to nondetectable levels by 100 days (median 50 days)
- HIT antibody formation does not recur more quickly or more often in a patient with previous HIT who is reexposed to heparin (no immune memory)

Management of patients with HIT requiring anticoagulation for CPB

- Previous HIT – HIT antibodies are no longer detectable
- Subacute HIT – A recent episode of HIT with detectable HIT antibody and resolution of thrombocytopenia
- Acute HIT - Thrombocytopenia with detectable antibodies +/- thrombosis

Previous HIT (nondetectable Ab)

- Proceed with surgery using standard heparinization
  - Avoid preoperative heparin completely
    - eg, perform heart catheterization using argatroban, bivalirudin, lepirudin, or danaparoid
  - After surgery, nonheparin anticoagulants should be used if antithrombotic prophylaxis is needed
    - Warfarin, danaparoid 750 U SQ bid-tid, lepirudin 15 mg SQ bid
- If urgent surgery and > 100 days since heparin exposure, considered safe to proceed with heparin

Acute or Subacute HIT

1. Postpone surgery until Ab undetectable
2. Off-pump technique using bivalirudin, lepirudin, argatroban, or danaparoid
3. On-pump technique with bivalirudin, lepirudin, argatroban, or danaparoid
4. Heparin (if platelet activation assay is negative +/- ELISA only weakly positive)

Argatroban

- Eliminated primarily by hepatic mechanisms, may be useful for patients with renal failure
- Successful reports of use for CPB, but clinical experience is limited
- Marked prolongation of INR can complicate initiating warfarin therapy post-op

Danaparoid

- Withdrawn from US market in April 2002
- Used in mid 1990s – use complicated by long half-life, significant hemorrhage, lack of antidote, difficulty in measuring levels

Lepirudin

- Has been used during CPB in more than 70 patients in published reports
- Problems with monitoring levels:
  - aPTT is adequate to monitor hirudin when treating thrombosis, aPTT-hirudin relation flattens at the high concentrations needed for CPB
  - ACT is prolonged, but does not correlate well with hirudin levels

Ecarin Clotting Time (ECT)

- A snake venom prothrombin activator-based assay
- Linear relationship is seen between therapeutic levels of lepirudin required for CPB and prolongation of ECT levels
- Can be obtained rapidly using whole blood supplemented with normal human plasma

  (Accuracy of ECT requires prothrombin levels at least 70% of normal. Hypoprothrombinemia from hemodilution during CPB requires supplementation of normal human plasma for a reliable test)

Lepirudin

- Target CPB lepirudin levels are between 3.5-4.0 mcg/mL
  - Levels >4.0 associated with increased post-op bleeding
  - Levels <2.0 increase risk of clotting in the CPB circuit
- 80% of lepirudin distributes in the extravascular space
  - Adjustments may be needed in patients who have received lepirudin pre-op

Lepirudin

- Additional lepirudin must be added to CPB circuit after coming off pump to prevent circuit clotting
  - must be washed prior to reinfusion to patient
- Repeat bolus infusions have been linked to anaphylaxis
- Major bleeding is a frequent problem with lepirudin use for CPB

Treatment Protocol for Hirudin (Lepirudin)
Anticoagulation during Cardiopulmonary Bypass

Initial lepirudin dosing (pre-CPB)
Initial IV lepirudin bolus: 0.25 mg/kg
and initiate continuous IV infusion*: 30 mL/hr (0.5 mg/min)
Lepirudin added to pump circuit volume: 0.2 mg/kg
Target lepirudin plasma level: >2.5 mcg/mL at start of CPB.
If <2.5 mcg/mL, give additional bolus (10 mg)

Lepirudin dosing and monitoring while on CPB
Continue IV infusion (adjusted as below): 30 mL/hr (0.5 mg/min)
Frequency of lepirudin level monitoring: every 15 minutes using ecarin clotting time
Lepirudin plasma level dosing modification:
>4.5 mcg/mL: reduce infusion rate by 10 mL/hr
3.5-4.5 mcg/mL: no change in infusion rate
<3.5 mcg/mL: increase infusion rate by 10 mL/hr

Special steps toward end of CPB
Stop lepirudin infusion 15 minutes before anticipated end of CPB
After separation from CPB, administer 5 mg lepirudin to the pump circuit to prevent clot formation

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*50 mg of lepirudin dissolved in 50 mL 0.9% sodium chloride

Bivalirudin

- Short half-life (25 minutes) and predominant enzymatic elimination are advantageous for use in CPB
- In spite of enzymatic breakdown, clearance is reduced ~80% in dialysis-dependent patients
- Extracorporeal hemoconcentration can remove up to 70% of circulating bivalirudin prior to reinfusion to patient

Bivalirudin

- As with lepirudin, ECT is recommended for intraop monitoring during CPB
  - Anecdotal successes (and some failures) using ACT monitoring
  - For OPCAB (lower concentrations), ACT can be used

Bivalirudin

- Sensitivity to enzymatic breakdown dictates avoidance of surgical techniques that allow blood to stagnate, which increases protease activity
- Presence of a visible thrombus in stagnant blood (eg, pericardial cavity) does not indicate a need for additional anticoagulation of circulating blood

Bivalirudin

- Hypothermia reduces bivalirudin proteolysis
  - Patient core temperature should be returned to at least 37° at the end of CPB
  - Patient temp should be maintained by active measures during recovery

Bivalirudin

- In case of need to return to CPB, circuit clotting must be prevented
  - A cross-limb is added to the bypass circuit during set-up, which remains clamped until coming off bypass
  - Bolus of bivalirudin is added to the circuit and contents are recirculated to prevent clotting
- After successful separation, pump contents can be washed with cell saver and reinfused

Treatment Protocol for Bivalirudin Anticoagulation During Cardiopulmonary Bypass

Initial bivalirudin dosing (pre-CPB)

Initial IV bivalirudin bolus: 1.5 mg/kg
and initiate continuous IV infusion: 2.5 mg/kg/hr (42 mcg/kg/min)
Bivalirudin added to pump circuit volume: 50 mg
Target bivalirudin plasma level: >10 mcg/mL at start of CPB
If <10 mcg/mL, give additional bolus (0.25 mg/kg) and increase infusion rate by 0.25 mg/kg/hr

Bivalirudin dosing and monitoring while on CPB

Continue IV (adjusted as below): 2.5 mg/kg/hr or greater (as above)
Frequency of bivalirudin level monitoring: every 30 minutes using ECT
Intraoperative dose adjustments, based on ECT*

Bivalirudin plasma level (ECT)*	*Dosing modification*
>15 mcg/mL (>500 secs)	Reduce infusion rate by 0.25 mg/kg/hr
10-15 mcg/mL (400-500 secs)	No chance in infusion rate
<10 mcg/mL	Give additional bolus (0.25 mg/kg) and increase infusion rate by 0.25 mg/kg/hr

Special steps at end of CPB

Stop bivalirudin infusion at end of CPB, then either:

1. *Within 10 mins* of stopping bivalirudin infusion: first reinfuse pump volume to patient, and then give 25-mg bivalirudin bolus to the circuit to prevent clotting and continue to recirculated (repeat 25-mg bivalirudin boluses to circuit every 20 mins); any subsequent reinfusion of pump volume to the patient should be processed through a cell saver to remove bivalirudin; or
2. Promptly empty pump volume into cell saver (replacing with crystalloid), thus avoiding need for postseparation bivalirudin boluses to circuit; process blood for reinfusion with cell saver to remove bivalirudin

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The target bivalirudin concentration (10-15 mcg/mL) corresponds to an ECT of 400-500 sec using the RapidPoint Coag (Bayer); with other ECT methods, the bivalirudin concentration should be determined using a calibration curve.

Bivalirudin – The Next Heparin?

- Has compared favorably in randomized trials against heparin in non-HIT patients undergoing off-pump surgery
- Currently under investigation in phase 3 multicenter trials comparing bivalirudin with heparin for on- and off-pump cardiac surgery in patients with and without HIT

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